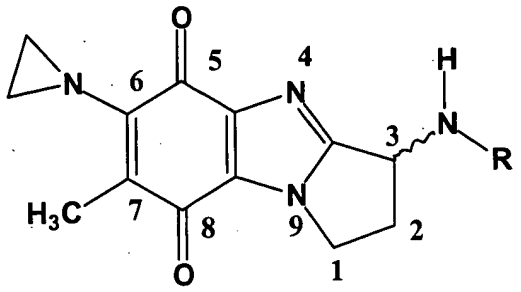
## REMARKS

The presently claimed invention relates to the use of certain compounds in the treatment of neoplastic of neoplastic disease, denominated by the inventor as "yujungamycins". The compounds have the structure shown below, wherein R can be a number of different substituents.




The compounds are derivatives of 6-aziridinyl-3-aminopyrrolo[1,2-*a*]benzimidazole-5,8-dione, and are characterized by having a substituted nitrogen at the 3 position of the ring. (The designation "3 position" is determined by the rules of the International Union of Pure and Applied Chemistry (IUPAC).) In support of this, please see page 6, lines 17 et seq. of the specification.

More specifically, the invention relates to the use of these compounds in the treatment of neoplastic disease, which the inventor has determined have unexpectedly excellent properties against neoplastic tissue in animal (mammalian) models. For example, see pages 8, lines 11-14, and page 9, lines 12+.

Claims 1-10 have been deleted and replaced with new claims 11-22. The new claims substantially incorporate the subject matter of the original claims, but also include new claims drawn to two of the compounds described in the application which are novel. The specification

has also been revised pursuant to suggestions by the Examiner.

The Examiner has noted several informalities in the specification and claims. In response, Applicant has herein deleted the figures at pages 8, 9, 10 and 11 of the specification, and has added them as freestanding formal drawings, as suggested by the Examiner. Further Applicant has amended the specification to insert a section titled "Brief Description of the Drawings". In addition, original "Scheme 2" at page 5 has been deleted, and replaced with a clearer version. No new matter has been added by the foregoing amendments.

It is believed that the new claims submitted herewith have rendered moot the objections to informalities in the claims as set forth in the Office Action.

**Written Description Objection**

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph, on the grounds that it allegedly contains subject matter not described in the specification in such a way as to reasonably convey to one of skill in the relevant art what is meant by the term yujungamycins. This rejection has been carefully considered, and is most respectfully traversed for the reasons discussed below.

Yujungamycins are characterized as having the azamitosene core structure shown at page 2, line 11 of the specification, wherein the "Z" substituent is a Nitrogen-containing group (i.e., yujungamycins have a substituted nitrogen at the 3 position of the ring. The application conveys to one of skill in the art the general structure of yujungamycins, and further describes specific yujungamycins. In this regard, Applicant points to the specification at page 6, lines 16 et seq.,

wherein it is described that yujungamycins all bear a nitrogen bound to the 3-position of the ring. As noted in the specification at page 3, line 7, Scheme 1 and Scheme 2 demonstrate the preparation of yujungamycins. Moreover, the amendments to the claims are believed to overcome the rejection.

Claims 1, 9 and 10 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. The Office Action states that the scope of the term "yujungamycin" is unclear. As noted above, yujungamycins have the core structure shown throughout the specification, and all are N-substituted at the 3-position.

It is also believed that the amended claims render moot the rejection of claims 9 and 10 for alleged lack of antecedent basis for a "pharmaceutical preparation".

Claim 1 stands rejected under 35 U.S.C. § 102(b) as begin anticipated by U.S. Patent No. 5,246,955 (Skibo et al.). The Office Action states that the term "yujungamycin" would encompass compounds having the azamitosene core structure, regardless of substitution. This rejection has been carefully considered, but is respectfully traversed. There are no yujungamycin compounds described in Skibo '955, and therefore there is no anticipation by this prior art. In this regard, Applicant points out that the closest compounds disclosed in Skibo '955 contain an oxygen atom at the third position of the ring. In contrast, the presently claimed compounds all require that there be nitrogen at the third position. Thus, there is simply no anticipation.

Claims 1-7, which were drawn to pharmaceutical preparation for treating neoplastic

disease, stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Skibo et al. ("Studies of Pyrrolo[1,2-α] benzimidazole quinine DT-Diapharose Substrate Activity...", *J. Med. Chem.*, Vol. 40, pp. 1327-1339 (1997). This rejection has been carefully considered, and is respectfully traversed for the reasons set forth below.

The cited reference discloses *in vitro* tests (i.e., cell line tests) on a particular yujungamycin (denoted compound no. 3 in the reference). However, the reference fails to disclose or teach the two compounds presently set forth in claims 15-17. Moreover, while the reference discloses tests of *in vitro* activity of compound no. 3, the reference fails to disclose a pharmaceutical preparation for administration to animals or humans comprising its compound no. 3. Certainly there is no teaching in the cited reference for treating animals, because one of skill in the art understands that a compound which shows good activity *in vitro* against cancer cell lines does not necessarily have good activity *in vivo* against cancerous tumors, not to mention that good *in vitro* tests give little to no indication whether administration to an animal or human will prove lethal to the subject. Generally speaking, it is very difficult to predict how any given compound will react in the body of an animal or human subject, due to numerous factors, such as the subject's own enzymes, its immune response, etc. Certainly there is no teaching or suggestion in the reference that would lead one of skill to treat cancer in humans and animals with compounds not even disclosed in the reference.

The Office Action seems to urge that methanol and buffer solutions for enzymatic *in vitro* studies as discussed in the Skibo publication anticipate the Applicant's claims to its

pharmaceutical preparation for treating neoplastic disease. It is respectfully requested that the Patent Office advise where in the prior art one is taught to use a buffer solution for an enzymatic assay for administration to an animal or human. Thus, claims reciting a "pharmaceutical preparation for administration to an animal or human subject, for the treatment of neoplastic disease in the subject", are not anticipated. Accordingly, it is respectfully submitted that this rejection of claims 1-7 under 35 U.S.C. § 102(b) should be withdrawn.

**Rejection Under 35 U.S.C. § 103(a)**

Claims 7-10 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Skibo et al., *J. Med. Chem.* (1997). This rejection has been carefully considered and is respectfully traversed.

Claims 7-10 are drawn to pharmaceutical preparations for treating certain neoplastic diseases. The Office Action acknowledges that the prior art does not disclose treating a host afflicted with a neoplastic disease (such as ovarian cancer) but urges that the testing of a compound on ovarian cancer cell lines *in vitro* is sufficient to render obvious to one of ordinary skill in the art that use of that compound for the actual therapeutic treatment of mammals and humans. Applicant respectfully disagrees.

Firstly, one of ordinary skill in the art understands that there is little to no predictability from the results of *in vitro* tests to actual use *in vivo*. It is common for a compound showing terrific efficacy *in vitro* against cell lines to be entirely lethal to the animal models to which it is administered. Conversely, as in the present case, from time to time it is a compound showing little to no efficacy *in vitro* that ends up possessing remarkably beneficial results *in vivo*. While

one of skill in the art will initially screen compounds using *in vitro* tests, in an attempt to identify at least some beneficial activity, one of skill simply does not expect that *in vitro* testing models are predictive of *in vivo* success. Were this the case, we would have hundreds and hundreds of effective anticancer drugs available to patients today, because there are so many compounds which initially, *in vitro*, exhibit good efficacy against cancer cell lines.

The present inventors discovered unexpectedly that, despite the cited published reference showing that its compound 3 possessed low cytotoxicity in cell lines (see application at page 2, first full paragraph), compound 3 unexpectedly it showed high cytotoxicity against tumors *in vivo*. As discussed in the specification at page 6, first full paragraph, the invention rests in part of the inventor's recognition that to have a compound that has the greatest chance of having antitumor activity and the least chance of toxicity to the animal or human subject, there must be a suitable balance between the compounds polarity and lipophilicity. This invention surely is not disclosed or suggested by the prior art, and thus reconsideration and withdrawal of the rejection is requested.

In view of the foregoing, favorable consideration of the claims and allowance thereof is earnestly solicited. The Examiner is invited to telephone Applicant's undersigned representative if he believes that it would in any way facilitate prosecution of this application.

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Respectfully submitted,

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I hereby certify that this paper and all documents and any fee referred to herein are being deposited on the date indicated above with the U.S. Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10, postage prepaid and addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Louis A. Lofredo, Legal Assistant

8-2-04
Date of Signature